Remarks

Claims 1-7, 16, 23, 26, and 31-44 are pending, with claims 1-4 and 41-42 being the independent claims. Claims 3-7, 23, 26, 31, and 33-44 are withdrawn.

Claim 1 has been amended. Support for the amendment may be found throughout the Specification, *inter alia*, in the claims as originally filed. No new matter has been added. Applicants respectfully request that the proposed amendment be entered.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Withdrawal of Pending Claims 41-44

On page 1 of the Office Action, the Examiner has included claims 41-44 as withdrawn from consideration for allegedly being drawn to non-elected inventions. However, Applicants respectfully submit that claims 41-44 were added as new claims in Applicants' previous reply filed September 14, 2010. The Examiner has not provided a reason for not considering pending claims 41-44. Therefore, Applicants respectfully request that the Examiner consider claims 41-44.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 1 was rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Not in acquiescence to the stated basis for this rejection, and solely in an

effort to advance prosecution of the present application, Applicants have amended claim 1 to recite "from the same antigen."

Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 103(a)

The rejection of claims 1, 2, 16, and 32 under 35 U.S.C. § 103(a) as allegedly being obvious over De Groot *et al.*, *Immun. Cell Biol.* 80:255-269 (2002) ("De Groot") in view of Paul, W.E., *Fund. Imunol.*, 5th Edition, Lippincott Williams & Wilkins, Philadelphia, 666-667, (2003) ("Paul") is respectfully traversed.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki,* 745 F.2d 1468, 1471-73 (Fed. Cir. 1984). As set forth in *Graham v. John Deere Co. of Kansas City*, "[u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." 383 U.S. 1, 17 (1966). This has been the standard for over 40 years, and remains the law today. *See KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1734 (2007). If, after these criteria are considered, the evidence indicates that the claimed invention is obvious over the prior art, it may be said that a *prima facie* case of obviousness have been established.

Applicants respectfully assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness because a person of ordinary skill in the art would not have arrived at the claimed invention based on the teachings of De Groot in view of Paul. De Groot is deficient as a primary reference for at least the following reasons.

The Examiner contends that De Groot allegedly discloses a method for identifying putative epitopes by identifying broadly conserved (cross-clade) epitopes across strains of infectious agents such as HIV-1. Office Action at page 3. Additionally, De Groot is alleged to teach that non-anchor residues of the most conserved sequences can be substituted. However, as conceded by the Examiner, De Groot does not disclose a method for identifying an epitope comprising a step of identifying a peptide comprising ***only conserved non-anchor residues***, as required by the present invention. *Id.*

The pending claims are drawn to a method for identifying a candidate peptide epitope which *induces cross-reactivity* in CTLs against other *non-identical* variants of the peptide epitope. De Groot does not teach or suggest the claimed method. De Groot merely discloses a prediction and validation of T cell epitopes from primary protein sequences using "immuno-informatics." De Groot discloses predicting T cell epitopes using bioinformatics tools such as EpiMatrix and Conservatrix, and validating the predicted T cell epitopes using well-established T cell assays such as the ELIspot assay, tetramer assay, and intracellular cytokine staining. *See* De Groot, for example, at page 255, right column. Thus, De Groot is focused on establishing a *minimum subset* of T cell epitopes, termed an "epitope ensemble," that is sufficient to enable the immune system to mount a protective response against an infectious agent in future infections. *See* De

Groot, for example, at page 259, left column, and page 263, right column. Therefore, De Groot simply discloses genome-wide searches for putative T cell epitopes and further validation of those epitopes, but provides no guidance regarding the claimed methodology for identification of putative, cross-reactive CTL epitope variants.

At best, De Groot discloses so-called "promiscuous epitopes" that are restricted by more than one MHC molecule and, as a result, can be recognized by T cell clones in a broad population represented by the different MHC types. *See* De Groot at page 261. However, such promiscuous epitopes do not *induce cross-reactivity* in CTLs against one or more variants of the peptide epitope. De Groot further suggests identifying epitopes that are recognized by different MHC superfamilies. Such epitopes can serve to obtain a "cocktail" vaccine having a broad population coverage. In sum, De Groot simply discloses epitopes which, either alone or in combination, may elicit broad MHC coverage. However, nowhere in De Groot is disclosed a method to *induce* CTL *cross-reactivity* against a number of variant peptide epitopes derived from a specific antigen by using a single candidate peptide epitope from the same antigen, as presently claimed.

Paul does not cure the deficiency of De Groot. Paul is relied upon for allegedly teaching that conservative substitutions at TCR contact residues of an epitope result in variants that retain their ability to be recognized by the same TCR. On the other hand, non-conservative substitutions at TCR contact residues result in loss of reactivity of the TCR for that epitope. Office Action at page 3.

However, Paul does not disclose or provide any guidance for implementing the claimed methodology for identification of a HLA class I-restricted peptide epitope that

induces T cell cross-reactivity against other variants of the peptide epitope. In fact, Paul expressly discloses

> The interaction of peptide ligand with T-cell receptor can be studied by introducing single substitutions of conservative amino acids at these contact residues, such as Glu for Asp, Ser for Thr, or Gln for Asn. The T-cell receptor readily distinguishes among peptides with these minor differences at a single residue, and the results have been revealing. Depending on affinity for the T-cell receptor, *closely related (altered) peptides can elicit very different responses in T cells.*

Paul at page 667, second paragraph (emphasis added).

Converting to the terminology of the present invention, the contact residues of Paul are the "non-anchor residues." In order to cure the deficiency of De Groot, Paul must teach that one or more amino acid substitutions at these non-anchor residues would generate peptide epitope variants which would cross-react with the same CTL as the original non-substituted peptide epitope. In contrast, Paul discloses that such substitution actually generates peptide variants that are recognized by CTLs that are not cross-reactive. Thus, it would not have been obvious to one of skill in the art, in possession of Paul, that a single peptide epitope could be used to *induce CTL cross-reactivity* against other variants of the peptide epitope. In fact, given the teachings of Paul, one of skill in the art would be directed away from using a peptide epitope to induce CTL cross-reactivity against peptide epitope variants. As such, Paul could actually be viewed to teach away from the claimed invention.

Since there was no teaching or suggestion of all the claim limitations in De Groot in combination with Paul, a *prima facie* case of obviousness is not established. Furthermore, the claimed invention clearly possesses unexpected superior properties over previously known methodology of De Groot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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